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# Request for grant of a patent

*(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)*

The Patent Office

Cardiff Road
Newport
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NP10 8QQ

1. Your reference — REP07543GB

2. Patent application number *(The Patent Office will fill this part in)* — 0400350.5 — 8 JAN 2004

3. Full name, address and postcode of the or of each applicant *(underline all surnames)* —
Cambridge University Technical Services Ltd.
The Old Schools
Trinity Lane
Cambridge CB2 1TS

   Patents ADP number *(if you know it)* — 8206484001

   If the applicant is a corporate body, give the country/state of its incorporation — UK

4. Title of the invention — Holographic Sensor

5. Name of your agent *(if you have one)* — Gill Jennings & Every

   "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* —
Broadgate House
7 Eldon Street
London
EC2M 7LH

   Patents ADP number *(if you know it)* — 745002

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

| Country | Priority application number *(if you know it)* | Date of filing *(day / month / year)* |
|---|---|---|

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

| Number of earlier UK application | Date of filing *(day / month / year)* |
|---|---|

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request? — YES

   Answer YES if:
   a) any applicant named in part 3 is not an inventor, or
   b) there is an inventor who is not named as an applicant, or
   c) any named applicant is a corporate body.
   Otherwise answer NO (See note d)

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

| | |
|---|---|
| Continuation sheets of this form | |
| Description | 6 |
| Claim(s) | 2 |
| Abstract | -SD |
| Drawing(s) | 9 +9 |

10. If you are also filing any of the following, state how many against each item.

| | |
|---|---|
| Priority documents | |
| Translations of priority documents | |
| Statement of inventorship and right to grant of a patent (Patents Form 7/77) | |
| Request for a preliminary examination and search (Patents Form 9/77) | |
| Request for a substantive examination (Patents Form 10/77) | NO |
| Any other documents (please specify) | |

11. I/We request the grant of a patent on the basis of this application.

For the applicant
Gill Jennings & Every

Signature

Date 08/01/03

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

PERRY, Robert Edward
020-7377 1377

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f) Part 7 should only be completed when a divisional application is being made under section 15(4), or when an application is being made under section 8(3), 12(6) or 37(4) following an entitlement dispute. By completing part 7 you are requesting that this application takes the same filing date as an earlier UK application. If you want the new application to have the same priority date(s) as the earlier UK application, you should also complete part 6 with the priority details.

# HOLOGRAPHIC SENSOR

## Field of the Invention

This invention relates to a sensor that is especially suitable for use in the form of a subcutaneous implant.

## Background to the Invention

WO-A-9526499 discloses a holographic sensor, based on a volume hologram. This sensor comprises an analyte-sensitive matrix having an optical transducing structure disposed throughout its volume. Because of this physical arrangement of the transducer, the optical signal generated by the sensor is very sensitive to volume changes or structural rearrangements taking place in the analyte-sensitive matrix as a result of interaction or reaction with the analyte. An optical detector (for example, a spectrometer or simply the human eye) is used to detect any change in an optical characteristic of the sensor.

An alternative method of production for a holographic sensor is disclosed in WO-A-9963408. A sequential treatment technique is used, wherein the polymer film is made first and sensitive silver halide particles are added subsequently. These particles are introduced by diffusing soluble salts into the polymer matrix where they react to form an insoluble light-sensitive precipitate. The holographic image is then recorded.

Such a holographic sensor is made by recording a hologram as a plane mirror which is holographed in a trough of suitable liquid. This arrangement may not always be effective if the sensor is used in an environment where there is considerable light scatter, e.g. subcutaneously. In addition, the optical detector must be placed at a particular position with respect to the sensor, in order to detect reflected light.

## Summary of the Invention

The present invention is based on a realisation that the problems described above can be addressed by recording the hologram as a non-planar mirror. The invention allows for the design of holographic sensors which can reflect incident light in an accurate and predetermined fashion. The invention may obviate the requirement for the optical detector to be "brought" to the sensor.

For example, the mirror may be a concave mirror. This allows a wide range of possible uses, e.g. as a small subcutaneous implant which can be conveniently interrogated using a fibre optic bundle. Furthermore, to overcome the major obstacle of the problem of light scatter, the replay wavelength range can be adjusted to extend well into the near infra-red (NIR).

Alternatively, the mirror may be capable of effecting retroreflection. For example, the hologram may be formed as a "corner cube" prism. In this way, incident light will be retroreflected. Retroreflector holographic sensors may, therefore, have a "cat's eye" effect on incident light.

Description of Preferred Embodiments

A holographic sensor of the type used in this invention generally comprises a holographic support medium and, disposed throughout the volume of the medium, a hologram. The support medium interacts with an analyte resulting in a variation of a physical property of the medium. This variation induces a change in an optical characteristic of the holographic element, such as its polarisability, reflectance, refractance or absorbance. If any change occurs whilst the hologram is being replayed by incident broad band, non-ionising electromagnetic radiation, then a colour or intensity change, for example, may be observed.

There are a number of basic ways to change a physical property, and thus vary an optical characteristic. The physical property that varies is preferably the size of the holographic element. This variation may be achieved by incorporating specific groups into the support matrix, where these groups undergo a conformational change upon interaction with the analyte, and cause an expansion or contraction of the support medium. Such a group is preferably the specific binding conjugate of an analyte species. Another way of changing the physical property to change the active water content of the support medium.

A holographic sensor may be used for detection of a variety of analytes, simply by modifying the composition of the support medium. The medium preferably comprises a polymer matrix, the composition of which must be optimised to obtain a high quality film, i.e. a film having a uniform matrix in which holographic fringes can be formed. The matrix is preferably formed from the

copolymerisation of, say, (meth)acrylamide and/or (meth)acrylate-derived monomers, and may be cross-linked. In particular, the monomer HEMA (hydroxyethyl methacrylate) is readily polymerisable and cross-linkable. PolyHEMA is a versatile support material since it is swellable, hydrophilic and widely biocompatible. A "smart" polymer is preferred , i.e. a material that responds to the presence of one or more specific analytes in its environment by, say, a change in volume.

Other examples of holographic support media are gelatin, K-carageenan, agar, agarose, polyvinyl alcohol (PVA), sol-gels (as broadly classified), hydro-gels (as broadly classified), and acrylates. Further materials are polysaccharides, proteins and proteinaceous materials, oligonucleotides, RNA, DNA, cellulose, cellulose acetate, polyamides, polyimides and polyacrylamides. Gelatin is a standard matrix material for supporting photosensitive species, such as silver halide grains. Gelatin can also be photo-cross-linked by chromium III ions, between carboxyl groups on gel strands.

The sensor may be prepared in the same way as has already been described in the PCT (WO) publications given in the "Background". A suitable arrangement for this purpose is shown in Figure 1 of the accompanying drawings. An alternative method is by silverless double polymerisation, as described in British Patent Application No. 0305590.2. The content of all these specifications is incorporated herein by reference.

The invention will now be described by way of example only, with reference to the accompanying drawings.

Fig. 1 shows how a hologram may be formed as a curved concave mirror. The term "concave" is used herein in a broad sense, to describe any arrangement that has a focusing effect. The mirror may be, for example, spheric, aspheric such as parabolic or it may comprise flat central and edge portions at an angle to each other. If such a mirror is made by the silverless double polymerisation method described above, there would be normally no liquid in the exposure bath in Fig.1.

Fig. 2 shows a process similar to that of Fig. 1, except that the mirror is in the form of a "corner cube" retroreflector. Corner cube prisms are well known

in the art and typically reflect any light entering the prism back towards the light source, regardless of the orientation of the prism. Generally, corner cube devices are such that incident light retroreflected *via* three total internal reflections. A retroreflecting holographic sensor is advantageous because the optical detector does not need to be placed at a particular position with respect to the sensor.

The use of retroreflecting devices in space is well known. For example, retroreflecting sensors were placed on the moon in order to reflect laser beams from Earth to make precise distance measurements. In a similar manner, a sensor of the invention which is capable of effecting retroreflection could be used to detect changes in atmospheric conditions (e.g. humidity, temperature, levels of carbon dioxide or other chemically active gases) on a planet with an atmosphere. Detection could be achieved by interrogating the sensor with a collimated light beam or other remote light source located on, for example, an orbiting craft. Such sensors may also be used to detect changes in underwater environments. For example, changes in the levels of pH or ions could be detected. It is envisaged that sensors of the invention may find utility in applications as far reaching as these.

As indicated above, a sensor of the invention is particularly suitable for use in conjunction with a unit, e.g. of optical fibres, whereby light can be transmitted to and from the hologram. For example, a suitable bundle of fibres, ending in a probe tip, is shown in Fig 3. In a particular embodiment, the probe is about 5 mm in diameter, with an internal ring of 6 fibres, defining a circle 1 mm across, surrounding a central fibre.

In the particular embodiment shown in Fig. 3, the central fibre leads to a spectrometer read-out (not shown) and the ring fibres are connected to a white light illumination source (not shown). An alternative arrangement comprises the "ring" fibres at the spectrometer end in a line, one above the other, to coincide with, or substitute for, the normal spectrometer slit.

Corner cube devices are such that, if the incident light is diverging, then the retroreflected light will continue to diverge, possibly resulting in a poor signal.

Thus, it may be desirable to ensure that incident light is collimated or converged. In the case of the fibre optic arrangement of Fig. 3, this may be achieved by placing a small convex lens (not shown) in front of the bundle.

The utility of the invention will now be described, with particular reference to Figures 4 and 5.

In Fig. 4, the hologram of Fig. 1 is shown interrogated in a non-scattering clear environment. The hologram here returns the light as if it were returning from the concave mirror (as used in Fig. 1) to make it. However, because it was made with a particular laser wavelength, it becomes in effect a monochromatic concave mirror. Furthermore if it was made in smart polymer, the replay colour will change with its environment. An alternative would be to make it with more than one, well separated laser wavelength, enabling it to sense different factors in its environment. For example, it could appear to be simultaneously acting as a green, red or blue concave mirror, with the separation between the wavelengths much greater than the wavelength shifts likely to occur as it acts as a sensor, giving say a range of greens or reds but never large enough to cause ambiguous results from wavelength overlaps. The ability of the sensor to give a well separated response to more than one analyte may be achieved using a sensor having a layered structure, each layer comprising a different material. Alternatively, the sensor may consist of different materials lying concentrically adjacent to each other throughout their depth.

The holographic concave mirror image focuses the coloured light onto the central fibre. A valuable feature of working on axis (unlike previous work with plane mirrors where the diffracted light was arranged to reflect off at a slightly different angle to the specularly reflected light) is that, as the diffracted wavelength changes, it remains focused on the central position.

Fig. 5 shows the same arrangement of Fig. 4, but in a diffusing environment. This is typical of a subcutaneous implant.

In use, the intention is not necessarily to track changes in intensity of the returning light. If as much as 99% of the light is lost due to scatter, then being able to track a small wavelength shift in the remaining 1% from a very highly diffracting implanted smart hologram may be satisfactory. In order to reduce the

problem of scattered light, it may sometimes be helpful to make the hologram with an off-axis concave mirror.

For use as an implant, the sensor may have to be covered with material to lessen rejection problems. This should not affect the detection of analytes found in the body, such as glucose or ions.

In a particular embodiment of the invention, the concave mirror hologram can have its centre removed or covered so that it is in the form of a ring. This is illustrated in Fig. 6, and in position in Fig. 7 (a side sectional view). In this embodiment, provided that the illumination is centred on the middle of the ring (i.e. as if the full concave mirror were present) and is spread sufficiently to cover its area then the holographic diffraction will continue to focus quasi monochromatic light to the centre just as it does with a full concave mirror image.

Other aspects of the invention are shown schematically in Fig. 8, where the concentric rings illustrate an arrangement for the detection of a variety of analytes.

In a similar vein, Fig. 9 shows a holographic sensor comprising two sections, A and B, each comprising a hologram formed as a corner cube prism. Sections A and B can be used to detect different analytes. Both sections reflect incident light back to the light source (e.g. the fibre optic bundle illustrated herein), and thus the sensor may be used to detect two analytes simultaneously.

CLAIMS

1. A sensor for the detection of an analyte, which comprises a holographic element comprising a medium and a hologram disposed throughout the volume of the medium, wherein an optical characteristic of the hologram changes as a result of a variation of a physical property occurring throughout the volume of the medium, and wherein the hologram is formed as a non-planar mirror.

2. A sensor according to claim 1, wherein the physical property is the size of the medium.

3. A sensor according to claim 1 or claim 2, wherein the optical characteristic is the reflectance, refractance or absorbance of the holographic element.

4. A sensor according to any preceding claim, wherein the analyte is present in blood.

5. A sensor according to any preceding claim, wherein the analyte is glucose.

6. A sensor according to any preceding claim, in the form of a subcutaneous implant.

7. A sensor according to any preceding claim, which additionally comprises a unit, e.g. comprising optical fibres, whereby light can be transmitted to and from the hologram.

8. A sensor according to any preceding claim, wherein the mirror image comprises one or more rings.

9. A sensor according to any preceding claim, wherein the mirror is a concave mirror.

10. A sensor according to any of claims 1 to 8, wherein the mirror is capable of effecting retroreflection.

11. A sensor according to claim 10, wherein the mirror is in the form of a corner cube prism.

12. A method of detection of an analyte, which comprises remotely interrogating, with light, the holographic element of a sensor according to any preceding claim; and detecting any change in an optical characteristic of the sensor.

13. A method according to claim 12, wherein the sensor is as defined in claim 10 or claim 11.

14. A method according to claim 13, for the detection of an analyte present in Earth's or another planetary body's atmosphere.

15. A method according to claim 13, for the detection of an analyte present in an underwater environment.

16. A method according to any of claims 12 to 15, wherein the light is collimated.

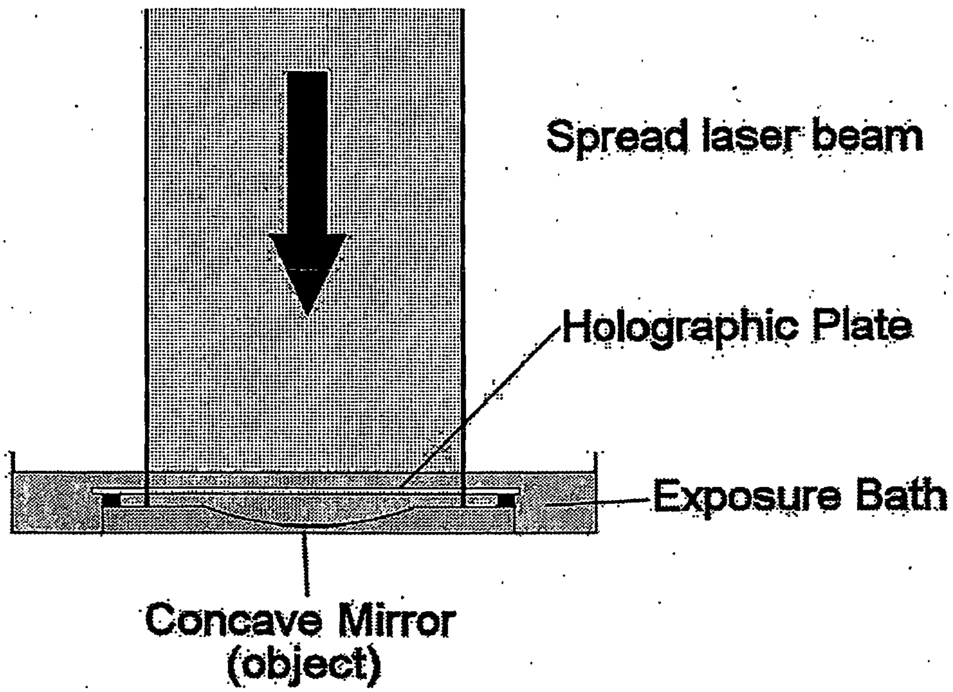
Spread laser beam
Holographic Plate
Exposure Bath
Concave Mirror
(object)

Figure 1

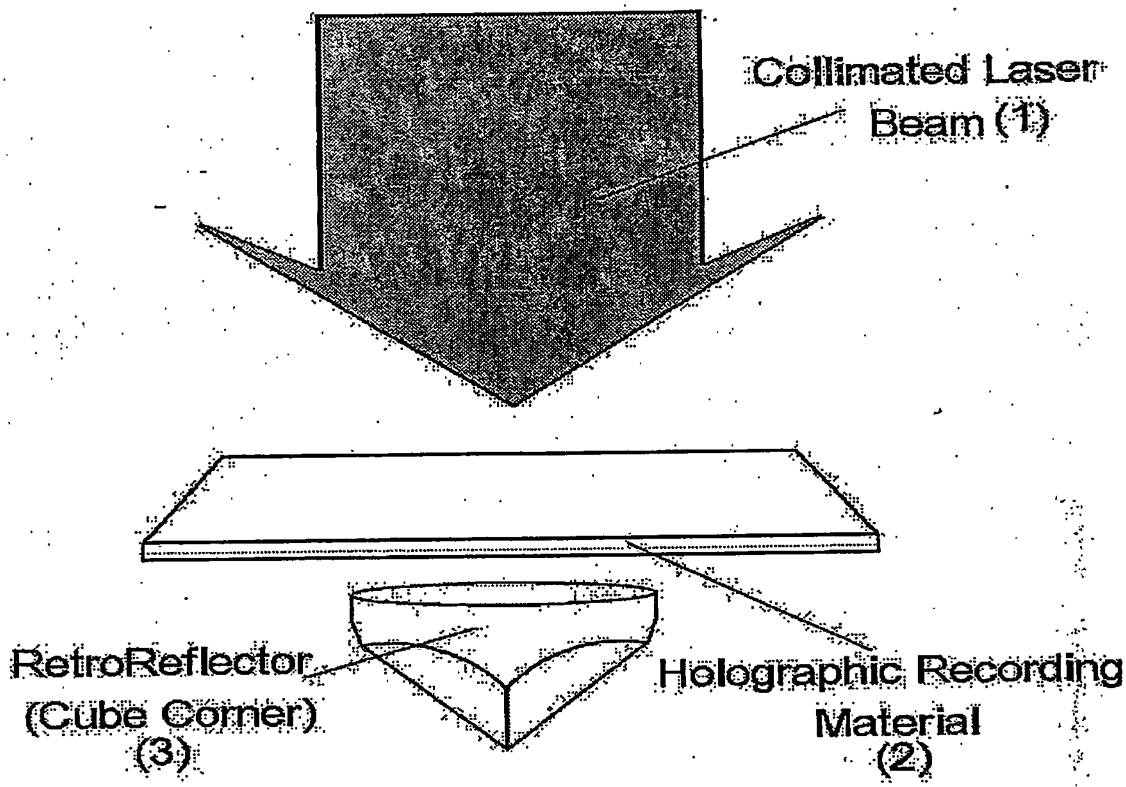
Collimated Laser Beam (1)
RetroReflector (Cube Corner) (3)
Holographic Recording Material (2)

Figure 2

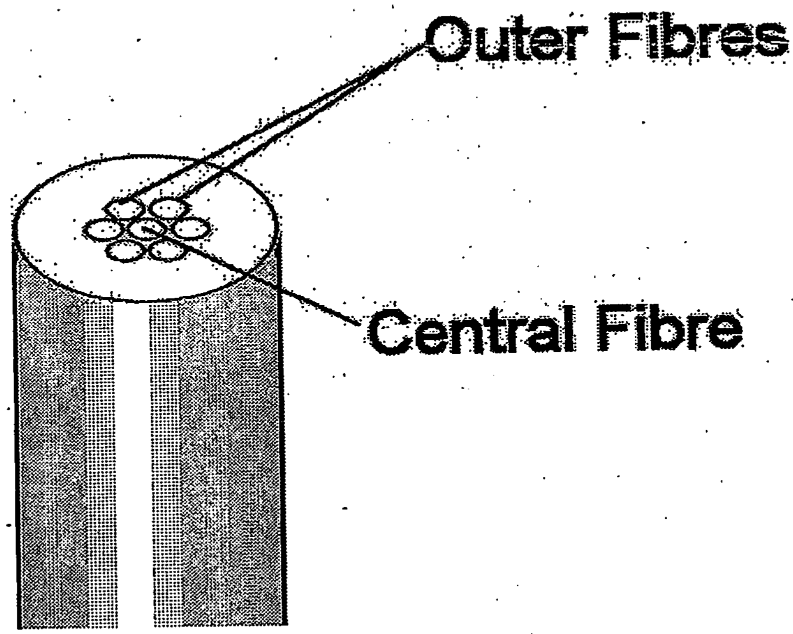


Figure 3

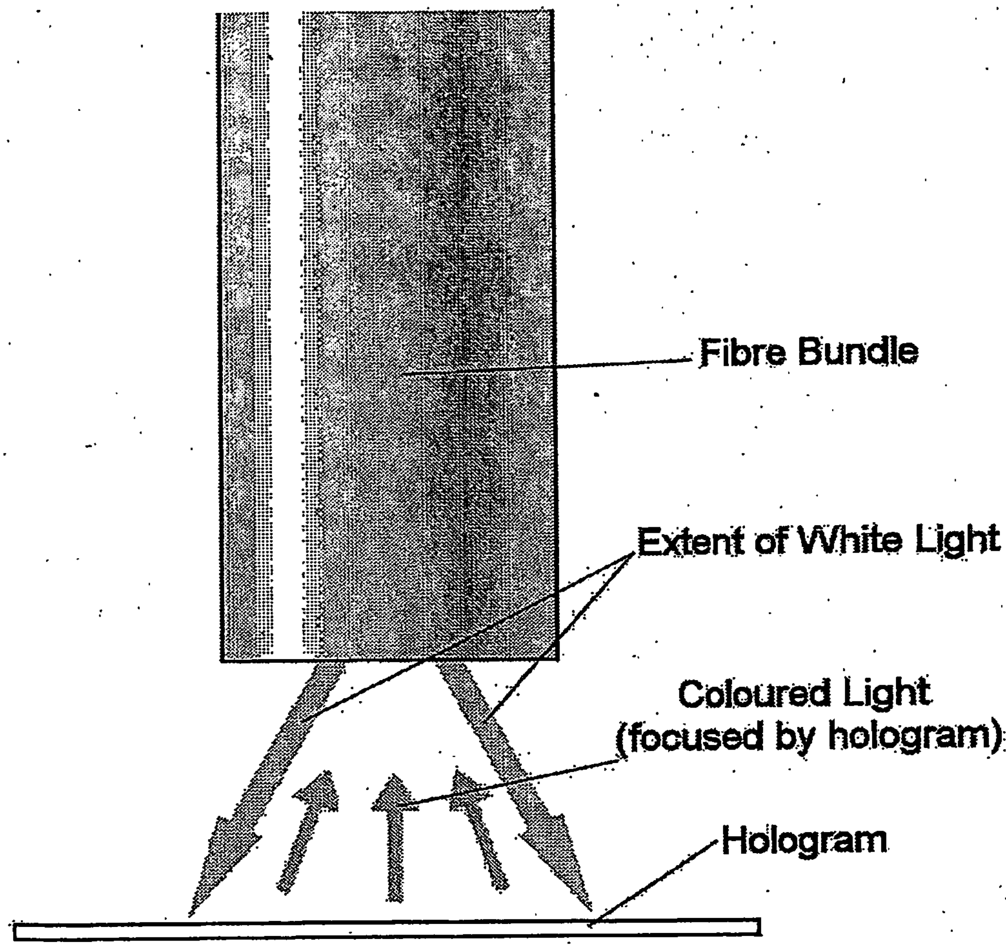
Fibre Bundle
Extent of White Light
Coloured Light
(focused by hologram)
Hologram

Figure 4

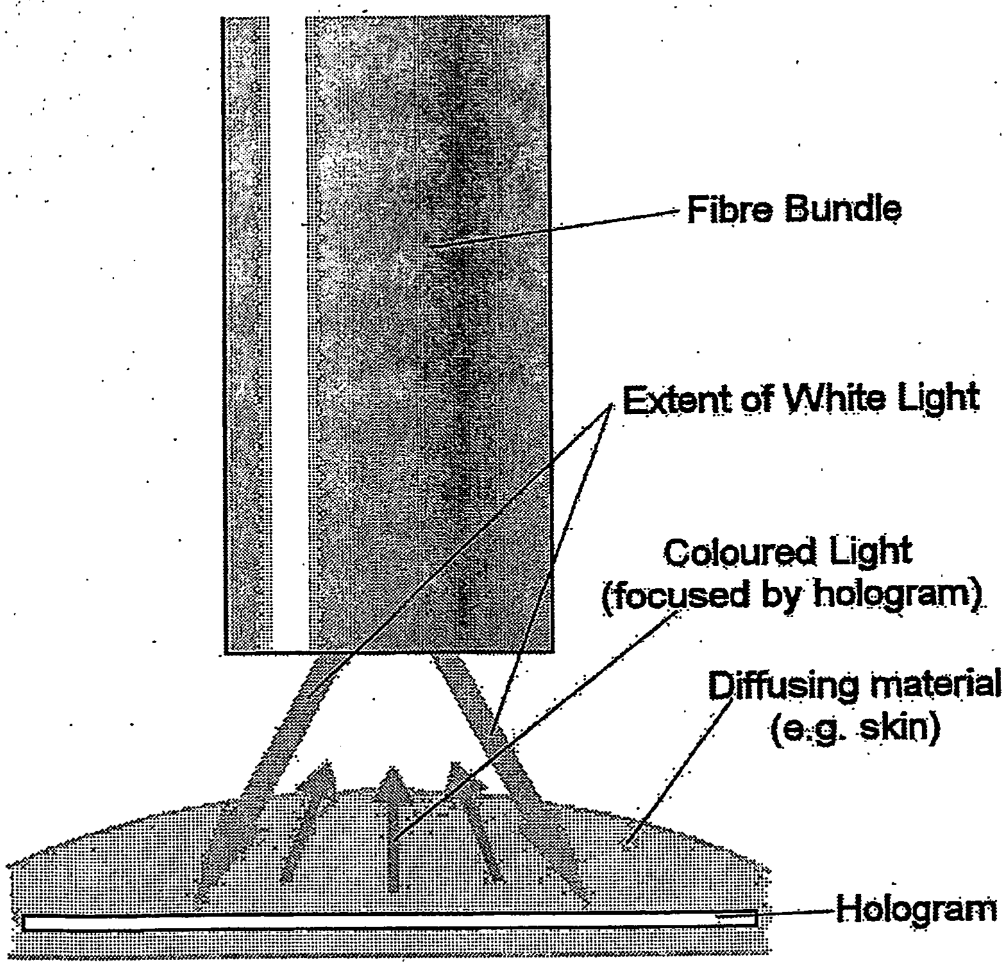
Fibre Bundle
Extent of White Light
Coloured Light
(focused by hologram)
Diffusing material
(e.g. skin)
Hologram

Figure 5

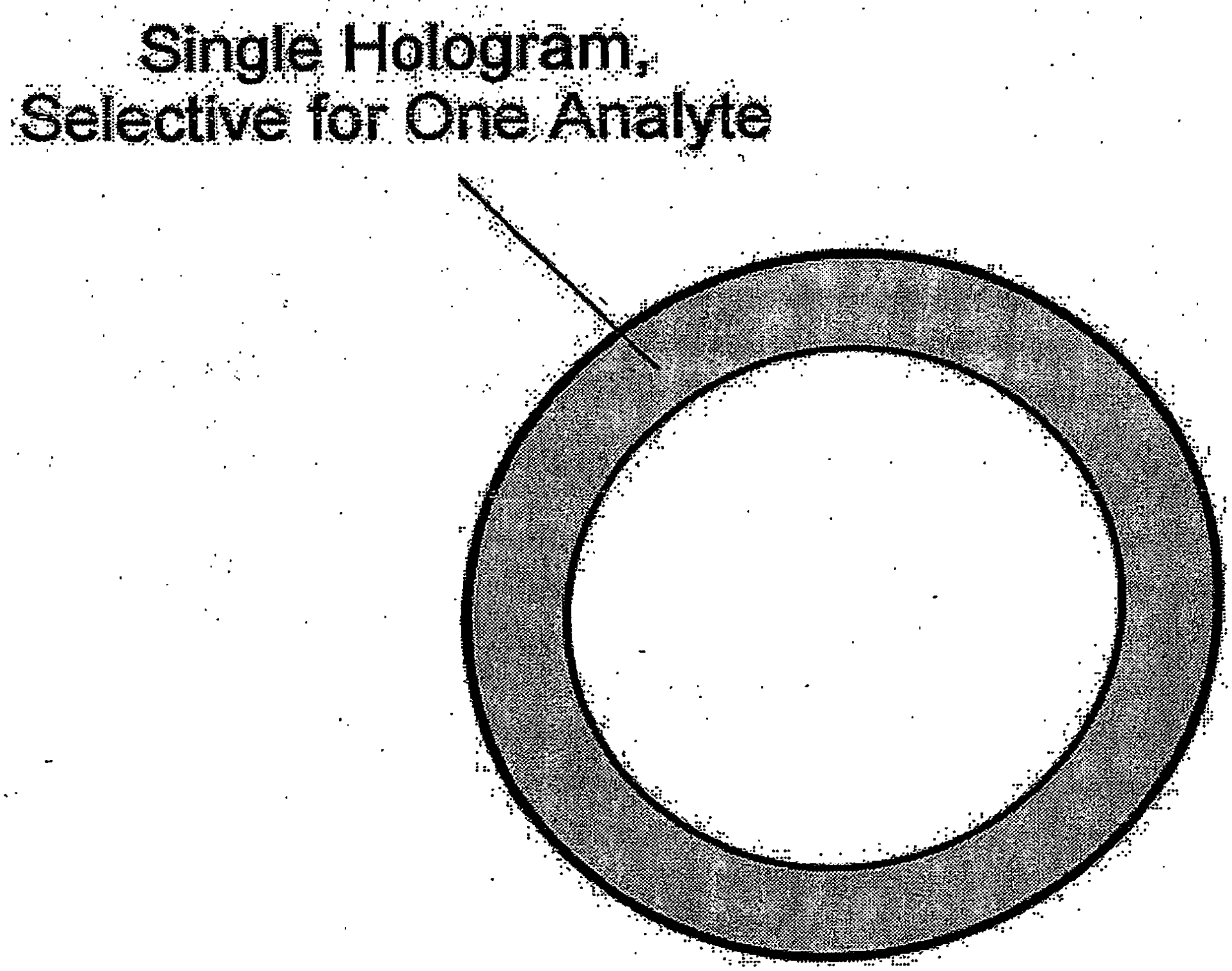


Figure 6

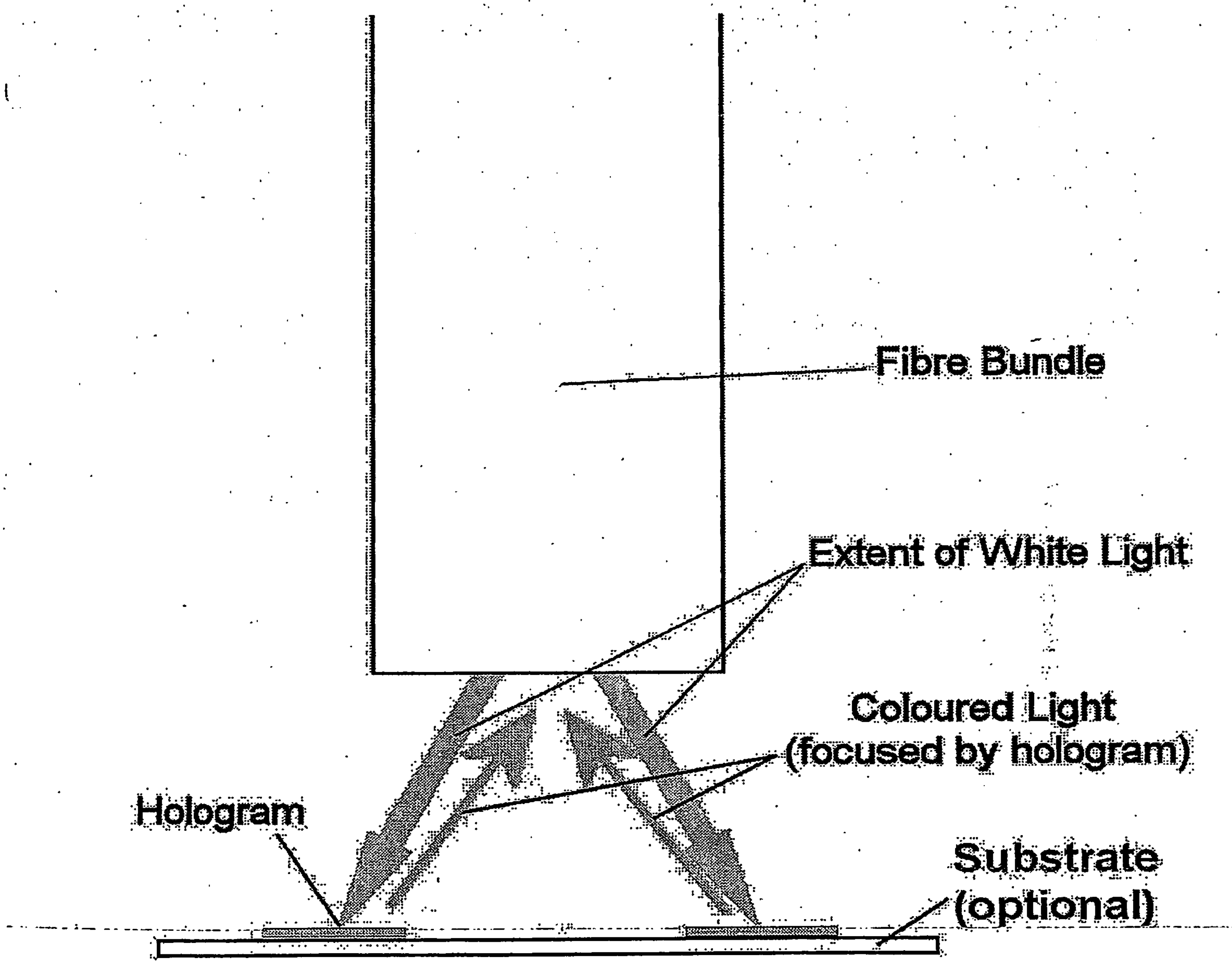
Fibre Bundle
Extent of White Light
Coloured Light
(focused by hologram)
Hologram
Substrate
(optional)

Figure 7

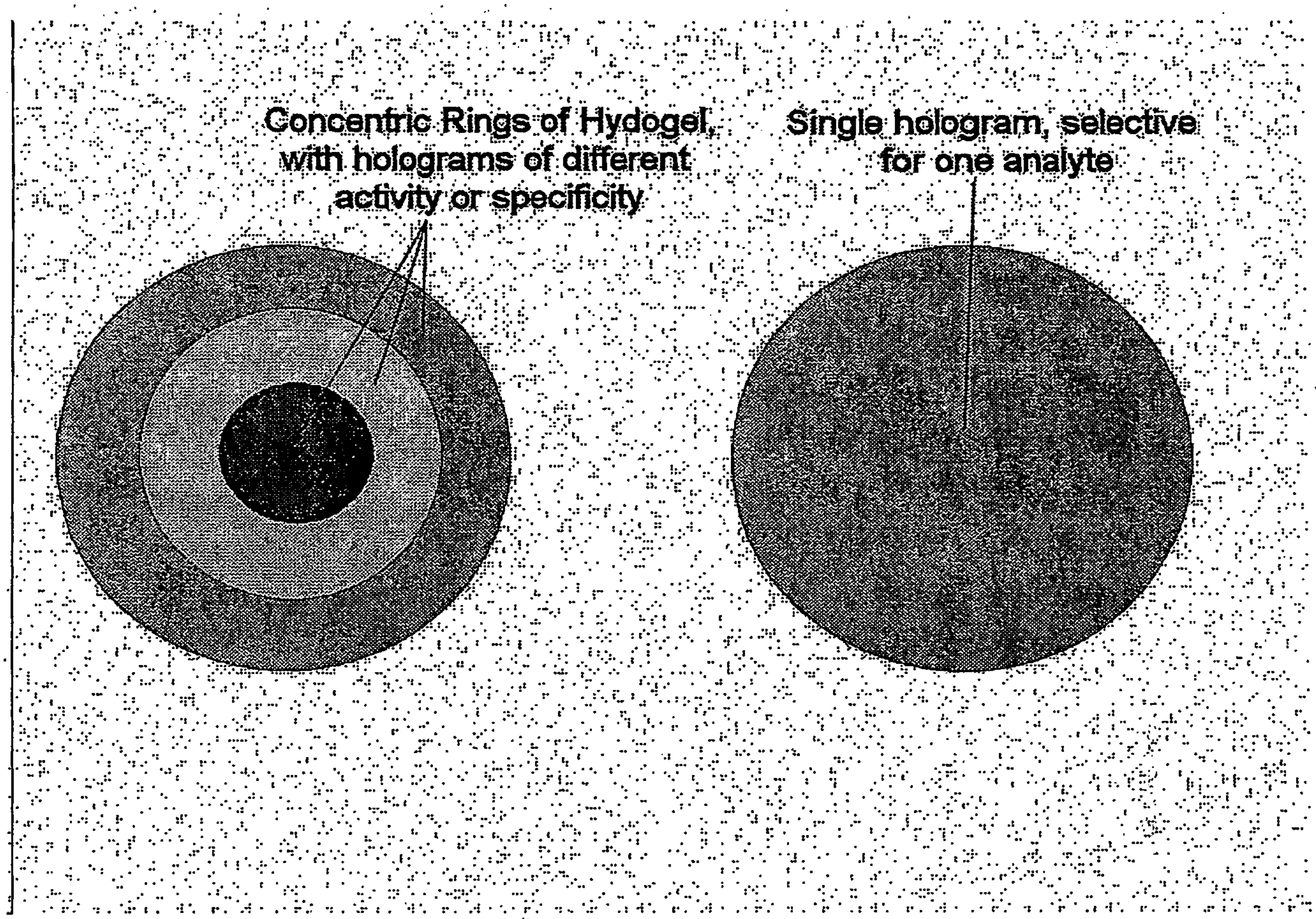
Concentric Rings of Hydogel, with holograms of different activity or specificity
Single hologram, selective for one analyte

Figure 8

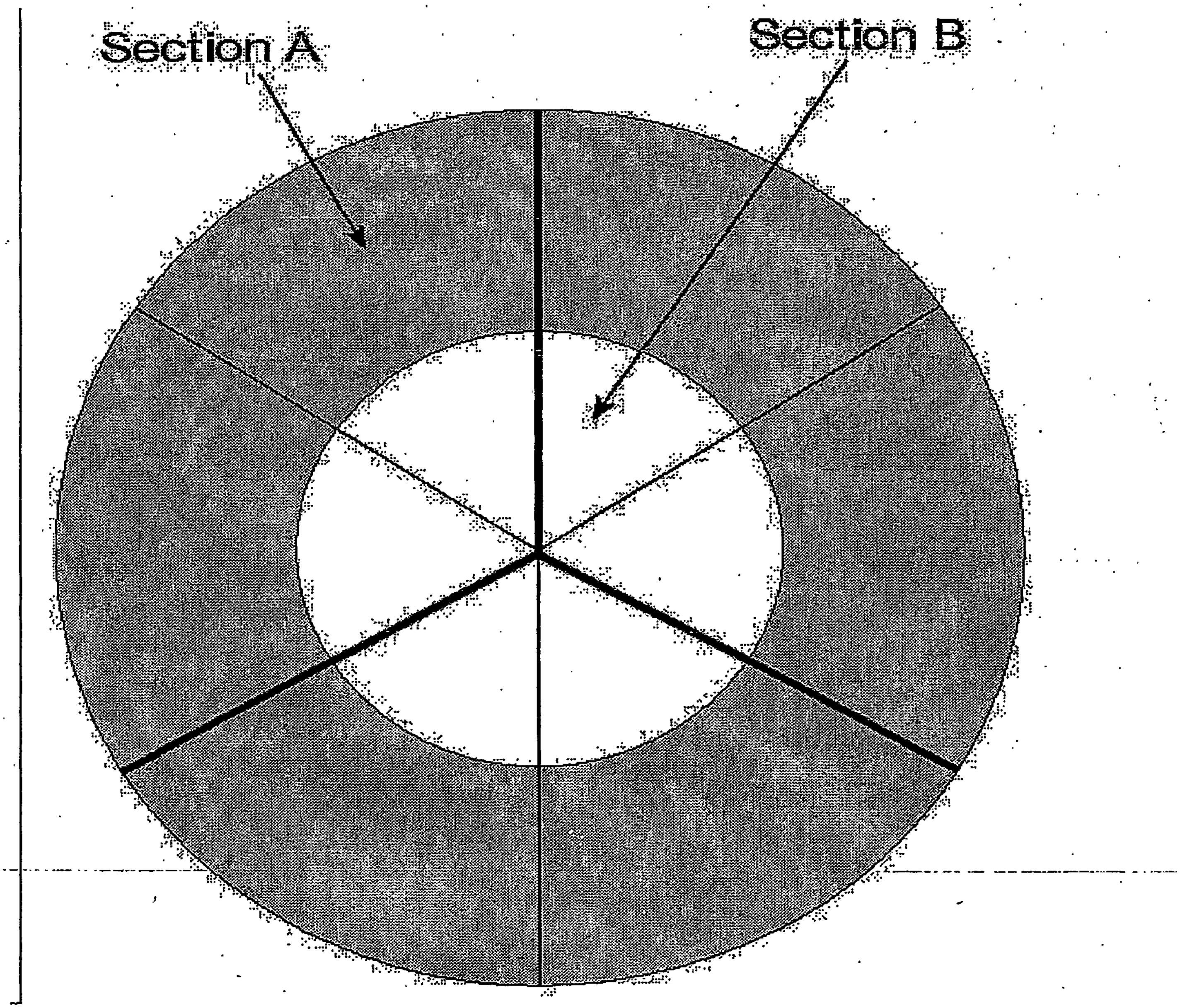


Figure 9